## REMARKS

Claims 1-78 were pending in the application. Claims 1-73 and 77-78 have been cancelled as being directed to non-elected inventions. New claims 79-96 have been added. Accordingly, after the amendments presented herein have been entered, claims 74-76 and 79-98 will be pending.

Support for the new claims can be found throughout the specification and claims as originally filed. Specifically, support for new claims 79-92 can be found, for example, at page 39, lines 15-29, of the specification. Support for new claims 93-94 can be found, for example, at page 14, lines 9-11, and lines 32-34 of the specification. Support for new claims 95-98 can be found in the claims as originally filed.

*No new matter has been added.* The foregoing claim amendments and cancellations of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and were done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

## Objection to the Sequence Listing

The Examiner has objected to the specification and drawings for failing to comply with 37 C.F.R. 1.821-1.825. Specifically, the Examiner states that, "this application fails to comply with the requirements of 1.821-1.825 for the reasons set forth herein. This application discloses an amino acid and nucleic acid sequences in Figures 3-7, pp. 4, line 29, pp. 16 lines 8 and 28, pp. 17, line 27, [and] pp. 18, line 13."

Applicants have amended the sequence listing to add the sequences presented in Figures 3-7, and have submitted replacement Figures 3-7 containing SEQ ID NOs for these sequences.

The sequences presented at page 4, line 29, page 16, lines 8 and 28, page 17, line 27, and page 18, line 13 have not been added to the sequence listing, since these sequences fall outside the definition of sequences that are required to be included in a sequence listing. Specifically, 37 C.F.R. 1.821 states that "[n]ucleotide and/or amino acid sequences as used in 1.821 through 1.825 are interpreted to mean an unbranched sequence of four of more amino acids or an unbranched sequence of 10 or more nucleotides." Further, 37 C.F.R. 1.821 (a)(2) states that "[a]mino acids are those L-amino acids commonly found in naturally occurring proteins," and

that, "[t]hose ***amino acid sequences containing D-amino acids are not intended to be embraced by this definition***."

The sequences objected to the by Examiner presented in the specification are defined as containing D amino acid isomers (i.e., Xaa1-Xaa4 as defined as being D amino acid isomers). Therefore these sequences fall outside the definition of sequences that are required to be included in a sequence listing according to 37 C.F.R. 1.821 through 1.825.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this objection.

***Drawings***

The Examiner has objected to the drawings because, "Figure 2 contains 12 panels none of which are labeled (i.e., "2A-2L"), and Figure 8 contains two graphs and should be labeled "8A" and "8B"."

In response, Applicants submit herewith replacement drawings that are labeled as specified above. Applicants also submit herewith replacement drawings 3-7 that have been amended to add SEQ ID NOs where necessary. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this objection.

***Rejection of Claims 74-76 Under of 35 U.S.C. 112, First Paragraph***

The Examiner has rejected claims 74-76 under 35 U.S.C. 112, first paragraph because the specification, "while being enabling for a method for preparing Aβ(16-30)-hFc, does not reasonably provide enablement for preparing any therapeutic agents, any as of yet unspecified peptide-target protein combinations, or any agents containing D-amino acid." The Examiner asserts that:

> [t]he claims are drawn very broadly to a method of preparing a therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein. The language of said claims encompasses all known and unknown proteins which may be targets for an as of yet unidentified peptide.

The Examiner further asserts that:

> the specification fails to provide any guidance for the successful manufacture and/or use of a therapeutic agent comprising an immunoglobulin heavy chain

> fused via a linker or a direct bond to a peptide capable of binding a target protein other than Aβ(16-30)-hFc. Since the resolution of the various complications in regards to making and using a therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of formulations therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein.

Applicants respectfully traverse this rejection. The Examiner asserts that the specification fails to provide "any guidance for the successful manufacture and/or use of a therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein other than Aβ(16-30)-hFc." The Examiner further asserts that the "making and using of a therapeutic agent comprising an immunoglobulin heavy chain fused via a linker or a direct bond to a peptide capable of binding a target protein is highly unpredictable." The Examiner thus concludes that it would have required undue experimentation for the ordinary skilled artisan to practice the claimed invention.

The factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized in In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors include:

1. the breadth of the claims,
2. the nature of the invention,
3. the state of the prior art,
4. the level of one of ordinary skill,
5. the level of predictability in the art,
6. the amount of direction provided by the inventor,
7. the existence of working examples, and
8. the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The present claims are directed to a method of preparing a therapeutic agent by joining an antibody Fc region to a polypeptide that has the ability to bind a target molecule with, or without, a linker.

As summarized below, the specification provides ample guidance, including working examples, regarding how to make and use the claimed peptide conjugates. In addition, contrary to the Examiner's assertion, the art of linking therapeutic agents to immunoglobulin heavy chains was well established (i.e., not highly unpredictable) at the time of the present invention. Indeed, the Examiner has provided no evidence to support the asserted lack of predictability in the art. At the time of filing, the level of skill in the art with respect to peptide linking and fusing techniques was high, including the art of joining Fc regions with other peptides. For example, techniques for joining antibody Fc regions with heterologous peptides have been known in the art since the 1980's, (e.g., see USPN 5,116,964 (attached as Appendix A), WO 89/07142, WO 88/03145, and EP 171496B1. Thus, it would not have required undue experimentation for one of skill in the art to have practiced the presently claimed invention which calls for joining an Fc region to a heterologous peptide, either directly, or using a linker.

In addition, Applicants' disclosure provides extensive guidance and working examples with respect to how to make and use the present invention as claimed. The specification provides the accession numbers of a number of heavy chain constant regions. For example, Applicants provide the accession numbers for mouse IgG1, human IgG1, IgG2, IgG3, IgG4, and the location at which the heavy chain constant regions begin (see page 7, lines 23-35 of the specification). The specification also describes how one of skill in the art can prepare and isolate an antibody Fc region. For example, Applicants teach, starting at page 11, line 1, methods of producing antibody heavy chain constant regions using protein chemistry techniques and recombinant DNA techniques. Further, even without the teachings in the specification, the ordinary skilled artisan would have been able to rely on the enormous body of literature that existed relating to Fc regions of antibodies and techniques for linking such Fc regions to peptides. Moreover, the specification provides working examples using specific Fc regions (see, for example, Example 8) that can be used in the methods of the invention.

Methods for identifying peptides that have the ability to bind a target molecule also were both routine in the art and are described in the specification. For example, the specification teaches that such peptides can be identified using the methods described in WO 97/22617 (see page 37, lines 38-39). Moreover, several other techniques were well known in the art for testing

the ability of a peptide to bind a known target molecule. For example, the target protein can be used as "bait proteins" in a two-hybrid assay (as described in, for example, U.S. Patent No. 5,283,317; Zervos et al. (1993) *Cell* 72:223-232; Madura et al. (1993) *J. Biol. Chem.* 268:12046-12054; Bartel et al. (1993) *Biotechniques* 14:920-924; Iwabuchi et al. (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300) to identify proteins which bind to a target protein. Alternatively, biophysical techniques such as Biomolecular Interaction Analysis (BIA) (see, for example, Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345) or analytical ultracentrifugation (see, for example, Rivas, G., *et al.* (1999) *Methods* 19:194-212) can be used to determine the ability of a protein to bind a target protein. Such techniques are routine to one of skill in the art and would require no more than routine experimentation.

In addition, the specification provides ample guidance as to the composition of the linker that may join the antibody constant region to the target protein binding sequence. For example, Applicants teach that the linker may be a peptidic or heterobifunctional cross-linker such as, for example, succinimidyl 4-(maleimidomethyl cyclohexame-1-carboxylate (see page 8, lines 29-36 for a listing of possible heterobifunctional linkers). Applicants further teach that peptidic linkers of the invention may be comprised of amino acid residues with small side chains, e.g., alanine or glycine.

The requirement for enablement is not whether experimentation is necessary, but rather if such experimentation is undue. *In re Angstadt,* 537 F.2d 298, 504, 190 USPQ 214, 219 (CCPA 1976). In the instant case, Applicants provide a detailed description of how to make the claimed therapeutic agents represented by the formula I-L-P', including working examples. In addition, the level of skill and predictability in the art with respect to making such agents was high. Indeed, several techniques for making these compounds were well known in the art by the present filing date. Accordingly, Applicants respectfully submit that the present claims are fully enabled and request that the Examiner reconsider and withdraw the rejection.

***Rejection of Claims 74-76 Under 35 U.S.C. 112, First Paragraph***

The Examiner has rejected claims 74-76 under 35 U.S.C. 112, first paragraph as, "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically, the Examiner states

> [t]he claims require a "therapeutic agent" but teach a method of identifying said agent thus implying that the activity and/or structure and/or identity of the agent used is not known and it must be discovered prior to preparing said agent. The claims do not require the therapeutic agent to possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, the claims are drawn to a genus of agents that is defined by desired activity.
>
> Furthermore the art recognizes that "agent" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells, radiation, antibodies, antibody fragments, cyclic peptides; agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds.
>
> To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of desired activity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

Applicants respectfully traverse this rejection. Contrary to the Examiner's assertion, the therapeutic agent recited in the pending claims is ***not*** defined solely by activity. The claims specifically require that the therapeutic agent comprises have the formula I-L-P', where I is an immunoglobulin heavy chain, L is an optional linker, and P' is a peptide that is capable of binding to a target molecule. Each of these components has a definite art-recognized structure. In addition, each of these components is specifically defined in the specification. For example, I is defined, at page 7, lines 13-22, to mean the constant region of any immunoglobulin heavy chain, *e.g.*, $\gamma_1$, $\gamma_2$, $\gamma_3$, $\gamma_4$, $\mu$, $\alpha_1$, $\alpha_2$, $\delta$, or $\varepsilon$ heavy chain, or a fragment thereof. Indeed, the Written Description Guidelines issued by the U.S. Patent and Trademark Office explicitly acknowledge that antibodies have a well know structure. 66 Fed. Reg.1099. Specifically, The Guidelines state that the structures of the five classes of antibodies are well known.

L is defined, at page 8, line 25 through page 9, line 3, to mean a direct bond or agent that can link the immunoglobulin heavy chain constant region to a peptide capable of binding a target

molecule. P' is defined at page 37, lines 9-12 to mean a peptide capable of binding a target protein. Peptides and linking agents are known to have a particular structure. Therefore, the claimed therapeutic agent is defined in terms of a class of molecules that possess both a particular structure and function.

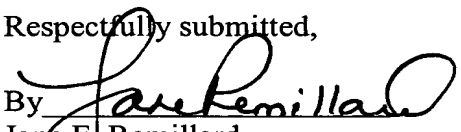
Finally, the Examiner states that the instant application fails to provide adequate written description and evidence of possession of any "agent." However, Applicants again respectfully point out that the claimed therapeutic agent is defined in terms of a particular structural genus, i.e., I-L-P', as well as the specific sequence of an exemplary member of the genus (see, for example, Example 8 which discloses the complete amino acid sequence of Aβ (16-30)-hFc). The specification further provides a structure/function mechanism whereby the target protein binding portion (P') binds to a target molecule and the Fc region will cause internalization and degradation of the target protein (see, for example, page 7, lines 7-12). Accordingly, it is respectfully submitted that the claimed therapeutic agents are sufficiently described under 112, first paragraph.

## SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Dated: September 23, 2004

Respectfully submitted,

By 

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